Cell therapy aims to prevent transplant rejection

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A cell therapy that could prevent transplanted organs being rejected, and remove the need for prolonged use of immunosuppressant drugs, has shown promise in early-stage studies in mice.

The approach would involve transplant patients being re-injected with their own immune cells after the cells have been isolated from a blood sample.

The cells would be grown in the laboratory under conditions that ‘teach’ the cells not to reject the transplant.

The University of Oxford research, funded predominantly by the Wellcome Trust and British Heart Foundation, is published in the journal Science Translational Medicine.

The scientists report that their approach using human immune cells can control or prevent rejection of a transplanted piece of blood vessel in a mouse model.

‘We have developed a new approach to generate cells called regulatory T cells that can control rejection of transplanted tissue in mice,’ says Dr Andrew Bushell of the Nuffield Department of Surgical Sciences at the University of Oxford, who led the work.

Transplantation is very effective and saves lives, but patients need to take powerful drugs for the rest of their lives to make sure the donated organ is not rejected by the body’s immune system.

Although these drugs have made successful transplantation possible, it is known that long-term use of immunosuppressants can lead to an increased risk of infection, cancer, damage to blood vessels, and metabolic complications.

‘Achieving a state where transplanted organs survive for a long time without immunosuppression is the holy grail in this field’ says Dr Bushell.

‘Many research groups across the world are trying to solve this problem because developing better ways to prevent transplant rejection is a big unmet clinical need.

Regulatory T cells may provide part of the answer.

’It is known that among the body’s immune cells which patrol the body looking for any infections or foreign invaders, there is a population of cells called regulatory T cells, or Tregs.

The cells dampen down immune responses when they are no longer needed and help to maintain the normal status quo in the body’s immune system.

‘Regulatory T cells are important in controlling the body’s immune responses,’ explains Dr Bushell.

‘The immune system is a bit like an army whose job is to defeat the enemy, such as invading bacteria or viruses.

But when the war is over, the soldiers need to be told to stop fighting or they could cause damage to the body.

This is what regulatory T cells do.

‘If we can grow regulatory T cells in the laboratory and teach them to turn off immune cells that are attacking a transplant, we may be able to use these cells to control transplant rejection.’

The Oxford team, along with colleagues from the Karolinska Institute in Sweden and University College London, have developed a new technique for generating Treg cells that can recognise donated tissue or organs.

Human T cells are isolated and cultured in the lab with an existing drug called cilostamide and cells from the tissue being transplanted.

The Oxford scientists show that cilostamide, already used widely in people with vascular problems, blocks a biological pathway and encourages the growth of Treg cells.

By culturing the immune cells with others from the donated tissue, the Tregs are taught to recognise the donor tissue and turn off rejection.

The researchers then showed that the human regulatory T cells produced using this method could control transplant rejection in a mouse model with a human-like immune system.

The Oxford study is one of three papers in Science Translational Medicine reporting progress towards immune cell therapies to prevent transplant rejection.

Together, they make it possible to see how such therapies might work, if successfully developed.

The cell therapy approach is likely to be used first in living donor transplantation, where for example a person donates a kidney to a relative, spouse or close friend.

This type of donation is now very widespread because of the shortage of organs from deceased donors.

Here, a blood sample would be taken from the patient a few weeks before the operation so that the Tregs could be grown and tested in the laboratory before being given back to the patient.

The transplant operation would then be carried out as normal and immunosuppressive drugs given to control early rejection.

But as the patient’s own Treg cells begin to control rejection, the drugs could be steadily withdrawn until they were no longer needed.

Cell therapy of this kind may also be possible in transplantation from donors who have recently died, for example in heart transplantation.

Here, transplantation would be carried out as usual while the patient’s own cells are grown in the laboratory and converted into Tregs.

The cells would then be given back to the patient after transplantation and the doses of immunosuppressive drugs reduced gradually as the Tregs take over the job of controlling rejection.‘

Different research groups are beginning to discover different ways of generating Treg cells,’ explains Dr Bushell.

‘The next steps for the field include working out which approach is best and understanding how these T cells regulate the immune response.’

Dr Bushell is keen to stress that although these cell therapies are not treatments that are just around the corner for transplant patients, the Oxford and Kings College groups are members of an EU-funded European consortium that is working on the various issues necessary to allow trials of cell therapy in human transplantation to begin within the next 3-5 years.

Dr Shannon Amoils, Research Advisor at the British Heart Foundation, which part-funded both studies, said: ‘It was 43 years ago this month that the UK saw its first human heart transplant.

Since then we’ve learned to safely control the immediate immune reaction to a new heart, but around half of heart transplants still fail after a decade due to gradual, chronic, rejection of the heart.

‘Currently transplant patients are given lifelong medication to dampen down immunity.

But these drugs affect the immune response throughout the body, increasing the chance of infection and cancer.

What we hope for is a new way to prevent rejection by fine-tuning the immune response locally around the new heart.

These important studies now show that, in principle, we can do this by making use of our own regulatory T cells – or ‘Tregs’ – which are the immune system's natural suppressors.

If the techniques used in these studies can be transferred to the clinic it could signal a move to replace long term use of immune-suppressing drugs.

This would be a huge step forward for transplantation, more than four decades since the revolutionary treatment began.’

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**Notes for editors**

* The paper ‘Functional regulatory T cells produced by inhibiting cyclic nucleotide phosphodiesterase type 3 prevent allograft rejection’ by Gang Feng and colleagues is to be published in the journal Science Translational Medicine on.
* We understand that this issue of the journal will include three similar papers reporting research on cell therapies for preventing rejection of transplanted organs: one from Oxford, one from King’s College London and one from a US group.
* A King’s College London press release on their study is available.
* The Oxford University study was funded by the Wellcome Trust, the British Heart Foundation and the European Commission.
* **The Wellcome Trust** is a global charitable foundation dedicated to achieving extraordinary improvements in human and animal health. It supports the brightest minds in biomedical research and the medical humanities. The Trust’s breadth of support includes public engagement, education and the application of research to improve health. It is independent of both political and commercial interests. [www.wellcome.ac.uk](http://www.wellcome.ac.uk)
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  It is one of the largest biomedical research centres in Europe, with over 2,500 people involved in research and more than 2,800 students, and brings in around two-thirds of Oxford University’s external research income. Listed by itself, that would make it the fifth largest university in the UK in terms of research grants and contracts.  
    
  Oxford is home to the UK’s top-ranked medical school, and partnerships with the local NHS Trusts enable patients to benefit from the close links between medical research and healthcare delivery.  
    
  14 winners of the Nobel Prize for Physiology or Medicine worked or were educated at Oxford, and the division is home to 29 Fellows of the Royal Society and 68 Fellows of the Academy of Medical Sciences.  
    
  The development of penicillin at Oxford ushered in the modern age of antibiotics, and the confirmation of the link between smoking and cancer has prevented many millions of deaths. Oxford continues to be at the forefront of medical research, whether it’s the genetic and molecular basis of disease, the latest advances in neuroscience, or clinical studies in cancer, diabetes, heart disease and stroke. Oxford has one of the largest clinical trial portfolios in the UK and great expertise in taking discoveries from the lab into the clinic.  
    
  A great strength of Oxford medicine is its long-standing network of clinical research units in Asia and Africa, enabling world-leading research on the most pressing global health challenges such as malaria, TB, HIV/AIDS and flu. Oxford is also renowned for its large-scale studies, including UK Biobank and the Million Women Study, which examine the role of factors such as smoking, alcohol and diet on cancer, heart disease and other conditions.